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Insulin resistance and its treatment by thiazolidinediones.

Lebovitz HE, Banerji MA.

State University of New York, Health Science Center at Brooklyn, 11203, USA.

Insulin resistance is a change in physiologic regulation such that a fixed dose of insulin causes less of an effect on glucose metabolism than occurs in normal individuals. The normal compensatory response to insulin resistance is an increase in insulin secretion that results in hyperinsulinemia. If the hyperinsulinemia is sufficient to overcome the insulin resistance, glucose regulation remains normal; if not, type 2 diabetes ensues. Associated with insulin resistance, however, is a cluster of other metabolic abnormalities involving body fat distribution, lipid metabolism, thrombosis and fibrinolysis, blood pressure regulation, and endothelial cell function. This cluster of abnormalities is referred to as the insulin resistance syndrome or the metabolic syndrome. It is causally related not only to the development of type 2 diabetes but also to cardiovascular disease. A major unresolved issue is whether there is a single underlying cause of this syndrome and, if so, what might it be? Several promising hypotheses have been proposed. There are some data to support the hypothesis that fetal malnutrition imprints on metabolic regulatory processes that, in later adult life, predispose to the development of the insulin resistance syndrome. Visceral obesity also has been a candidate for the cause of the syndrome. Whatever mechanism is ultimately found to be responsible, it will undoubtedly have both genetic and environmental components. Among the biochemical mediators that are likely to be responsible for the interference with insulin's effects on intermediary metabolism are free fatty acids and other products from adipose tissue. Recent data suggest that the substances stimulate serine phosphorylation of molecules involved in the initial steps of insulin action, thereby blocking the ability of these molecules to be tyrosine phosphorylated and initiate the subsequent steps of the insulin action cascade. The thiazolidinediones are a new class of agents that have been developed to treat type 2 diabetic patients. These drugs act as peroxisome proliferator-activated receptor gamma (PPARgamma) agonists. Following their binding to the receptor, the heterodimer molecule that contains the binding site is activated. The activated complex binds to the response elements of specific genes that regulate molecules that effect insulin action and lipid metabolism. These genes are either activated or inhibited. Specifically, the thiazolidinediones improve insulin action and decrease insulin resistance. The exact mechanism by which these agents decrease insulin resistance is not clear but they do decrease the elevated free fatty acid levels present in insulin-resistant patients and they appear to change the body distribution of adipose tissue. Treatment of insulin-resistant type 2 diabetic patients with thiazolidinediones not only improves glycemic control and decreases insulin resistance, it also improves many of the abnormalities that are part of the insulin resistance syndrome.

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the childhood onset of cutaneous photosensitivity in light-exposed areas, but skin lesions are milder and less disfiguring than those seen in CEP, PCT, HEP, and VP.

Prevalence: EPP is the most common form of erythropoietic porphyria. Three hundred case reports were published as of 1976. There is no racial or sexual predilection, and onset is typically in childhood.

Pathogenesis of the clinical findings: The peak light absorption range for porphyrins corresponds well to the wavelength of light (about 400 nm) known to trigger photosensitivity reactions in the skin of EPP patients. Light-excited porphyrins generate free radicals and $^1O_2$. Such radicals, notably $^1O_2$, may lead to peroxidation of lipids, and cross-linking of membrane proteins which, in erythrocytes, may result in reduced deformability and hence hemolysis. Interestingly, protoporphyrin, but not Zn-protoporphyrin, is released from erythrocytes following irradiation, which may explain why, unlike EPP, lead intoxication and iron deficiency are not associated with photosensitivity. Forearm irradiation in EPP patients leads to complement activation and polymorphonuclear chemotaxis. Similar results have been obtained in vitro, and these events may also contribute to the pathogenesis of skin lesions in EPP.

Symptoms and Signs

Symptoms are usually worse during spring and summer and occur in light-exposed areas, especially on the face and hands. Within 1 h of exposure to the sun, stinging or painful burning sensations in the skin occur and are followed several hours later by erythema and edema. Petechiae or, more rarely, purpura, vesicles, and crusting may develop and persist for several days after sun exposure. Some patients experience burning sensations in the absence of such objective signs of cutaneous phototoxicity. Artificial lights may also cause photosensitivity, especially operating theater lights. Intense and repeated exposure to the sun may result in oncolysis, leathery hyperkeratotic skin over the dorsae of the hands, and mild scarring. Gallstones, sometimes presenting at an unusually early age, are fairly common. Hepatic disease, although unusual, may be severe and associated with significant morbidity. Anemia is uncommon. There are no known precipitating factors and no neurovisceral manifestations.

Laboratory Findings

The biochemical hallmark of EPP is excessive concentrations of protoporphyrin in erythrocytes, plasma, bile, and feces but not in urine, owing to its poor water solubility. The bone marrow and the newly released reticulocyte/erythrocyte appear to be the major source of elevated protoporphyrin concentrations, although the liver may contribute in certain cases. Mild anemia with hypochromia and microcytosis may occasionally be seen. Mild hypertriglyceridemia also occurs with increased frequency in patients with EPP.

Diagnosis

Photosensitivity and the demonstration of elevated concentrations of free protoporphyrin in erythrocytes, plasma, and stools with normal urinary porphyrins establish the diagnosis. Fluorescent reticulocytes on examination of peripheral blood smear may also suggest the diagnosis.

Treatment

Avoidance of the sun and use of topical sunscreen agents may be helpful. Oral administration of β-carotene 120 to 180 mg/day may afford systemic photoprotection resulting in improved, though highly variable, tolerance to the sun. The recommended serum β-carotene level is 600 to 800 μg/dL; beneficial effects are typically seen 1 to 3 mo after the onset of therapy. The mechanism probably involves quenching of activated O_2 radicals.

ANOMALIES IN LIPID METABOLISM

Abnormal levels of blood or tissue lipids resulting from metabolic disorders that may be inborn or due to endocrinopathy, specific organ failure, or external causes.

HYPERLIPOPROTEINEMIA (HLP)

(Hyperlipidemia)

The **major plasma lipids**, including **cholesterol** (or **total cholesterol [TC]**) and the **triglycerides (Tgs)**, do not circulate freely in solution in plasma, but are bound to proteins and transported as macromolecular complexes called lipoproteins. The **major lipoprotein classes—chylomicrons, very low-density (pre-β) lipoproteins (VLDL), low-density (β-) lipoproteins (LDL), and high-density (α-) lipoproteins (HDL)**—although closely interrelated, are usually classified in terms of physicochemical properties (eg, electrophoretic mobility and density after separation in the ultracentrifuge). Tgs are the major lipids transported in the blood; between 70 and 150 gm enter and leave the plasma daily compared with 1 to 2 gm of cholesterol or phospholipid. Chylomicrons, the largest lipoproteins, carry exogenous glyceride from the intestine via the thoracic duct to the venous system. In the capillaries of adipose and muscle tissue, 90% of chylomicron glyceride is removed by a specific group of lipases. Fatty acids and glycerol, derived from hydrolysis of chylomicrons, enter the adipocytes and muscle cells for energy utilization or storage. The liver then removes the remnant chylomicron particles. VLDL carry endogenous glyceride primarily from the liver to the same peripheral sites (adipocytes and muscle cells) for storage or utilization. Lipases (similar to those that act on chylomicrons) quickly degrade endogenous glyceride into intermediate density lipoproteins **(IDL)** that are shorn of much of their glyceride and surface apoproteins. Within 2 to 6 h this IDL is degraded further by removal of more glyceride to LDL, which in turn has a plasma half-life of 3 to 4 days. VLDL is the main source of plasma LDL.

The fate of LDL is unclear: The liver removes about 60%, and active receptor sites have been found on the surfaces of hepatocytes and other cells that specifically bind to apolipoprotein B (the major LDL protein) and remove most LDL from the circulation. A small but important amount of LDL appears to be removed from the circulation by nonreceptor mechanisms; eg, ingestion by scavenger macrophages that may migrate into arterial walls where their cholesterol contributes to the formation of "foam cells" of the atherosclerotic plaque.

Hypercholesterolemia can result from overproduction of VLDL, increased conversion of VLDL to LDL, or defective clearance of LDL. Increased secretion of VLDL from the liver may be caused by obesity, alcohol excess, nephrotic syndrome, diabetes mellitus, or a genetic disorder; each condition can result in increased LDL and TC levels and often is associated with hypertriglyceridemia. Defective LDL clearance may be due to diminished numbers or abnormal function of LDL receptors. The degree of resulting hypercholesterolemia depends on the severity of the abnormal activity of the LDL receptors. Structural abnormalities in apolipoprotein B that diminish its binding to otherwise normal LDL receptors are another genetic cause of hypercholesterolemia.

When dietary cholesterol reaches the liver, elevated cholesterol concentrations suppress LDL-receptor synthesis; their reduced number results in higher levels of plasma LDL and TC. Saturated fatty acids also increase plasma LDL and TC levels; the mechanism of action is unknown but is believed to be related to reduced activity of LDL receptors. In the USA, dietary cholesterol and saturated fatty acid intake is high and is thought to account for almost 50 mg/dL of higher average blood levels of LDL—enough to increase significantly the risk of coronary artery disease **(CAD)**. Abnormal LDL receptor function also occurs on the basis of molecular defects in the protein structure of the receptors, which interfere with LDL binding; this is the usual mechanism of the genetic disorders described below.

Normal Plasma Levels of Total Cholesterol (TC) and Triglycerides

A normal plasma TC level is difficult to define. Prospective studies have shown that the incidence of CAD rises linearly with plasma TC, and that values previously considered normal in the USA are higher than those found among comparable populations with a low

incidence of atherosclerosis. In addition, evidence (from well-designed prospective clinical trials) shows that lowering elevated levels of TC (and LDL) reduces the risk of CAD.

The optimal plasma TC for a middle-aged adult is probably ≤ 200 mg/dL. In the past, **hypercholesterolemia** has often been defined as *a value above the 95th percentile for the population,* which ranges from 210 mg/dL in Americans < 20 yr old, to > 280 in those > 60 yr old. However, these limits are clearly excessive because of the known risk of cardiovascular disease at these levels. A consensus recommendation of the National Cholesterol Education Program **(NCEP)** defines *TC levels < 200 mg/dL as a goal, levels between 200 and 240 mg/dL as borderline high, and levels > 240 mg/dL as high-risk.*

After an initial health screen, the NCEP recommends **further evaluation** of all those with high-risk TC as well as those in the borderline range (200 to 240 mg/dL) if CAD is symptomatic or 2 or more CAD risk factors are present (male sex, high BP, smoking, diabetes, low HDL, family history of CAD before age 55). This evaluation should include assessment in the fasting state of the level of TC, LDL, HDL, and Tg. LDL is calculated by measuring the plasma TC, HDL, and Tg, and applying the formula LDL = TC − HDL$_c$ − Tg/5 (this formula is valid when Tg is < 400 mg/dL).

The NCEP recommends that **treatment decisions** be based on the derived level of LDL with the optimal goal of LDL at < 130 mg/dL. When LDL is > 130 mg/dL, a diet low in total saturated fat and cholesterol is the basis of treatment. When LDL levels remain between 130 and 160 mg/dL and the patient has CAD or 2 or more CAD risk factors, or when LDL levels remain > 160 mg/dL (even without added risk factors), drug treatment in addition to diet should be considered.

In contrast to plasma TC, it is unclear that plasma Tgs are independent risk variables; like TC, they vary with age and a concentration of > 250 mg/dL is considered abnormal. While hypertriglyceridemia has not clearly been related to CAD, it has been associated with diabetes, hyperuricemia, and pancreatitis.

As indicated below, even more information can be obtained about CAD risk by viewing the plasma TC in terms of the units of lipid transport—the lipoproteins—than by a simple measurement of TC. Sixty to 75% of plasma TC is transported on LDL, the levels of which are directly related to cardiovascular risk. HDL, which normally accounts for 20 to 25% of the plasma TC, is *inversely* associated with cardiovascular risk. HDL levels are positively correlated with exercise and moderate alcohol intake and inversely related to smoking, obesity, and the use of progestin-containing contraceptives. Studies show that CAD prevalence at HDL levels of 30 mg/dL is more than double that at 60 mg/dL, and high levels of LDL or low levels of HDL have been associated with increased CAD risk. These findings provide a cogent reason to determine whether elevated TC levels are due to increases in LDL or to "benevolent" HDL; both must be considered independently and together in evaluating an individual's risk for atherosclerosis. In countries or in groups (eg, lactovegetarians, Seventh Day Adventists) where TC and LDL cholesterol are low because of nutritional habits (marked reduction in ingestion of total saturated fats and cholesterol), HDL levels are often relatively low and the risk for CAD is low. In the USA-based Framingham Study, however, men and women with relatively normal LDL levels (120 to 160 mg/dL) with HDL < 30 mg/dL were at increased risk for CAD.

Laboratory Methods

A useful clinical appraisal of lipids can usually be made by determining plasma TC, HDL-cholesterol, and Tg levels after the patient has fasted for ≥ 12 h. The specimen should also be observed for a milky chylomicron layer after it stands overnight in a refrigerator at 40° C. **Plasma TC** may be determined by colorimetric, gas-liquid chromatographic, enzymatic, or other automated "direct" methods. Enzymatic methods are usually most accurate. **Plasma Tg** usually is measured as glycerol by either colorimetric, enzymatic, or fluorometric methods after hydrolysis to glycerol and formaldehyde. (For LDL measurement, see above.) **Lipoprotein electrophoresis** is useful only in dyslipidemia and

should be preceded by plasma Tg and TC measurements. Electrophoresis should be used only when Tgs or TC are elevated or abnormally low, and not for routine screening.

Treatment

See treatment of hyperlipoproteinemia type II, below.

Converting Hyperlipidemia to Hyperlipoproteinemia

Most elevations in TC and/or Tg are modest in amount and due primarily to dietary excess. More significant hyperlipidemia is the manifestation of a heterogeneous group of disorders differing in clinical features, prognosis, and therapeutic response. An excessive plasma level of any lipoprotein can result in hypercholesterolemia. Similarly, hypertriglyceridemia may result from increased levels of chylomicrons, VLDL, or both. This lack of specificity makes conversion from lipids or hyperlipidemia to lipoproteins or hyperlipoproteinemia useful. TABLE 83–3 describes such a conversion of hyperlipidemia into 5 types of hyperlipoproteinemia. Each represents a shorthand or jargon term for the increased plasma lipoproteins. Since each lipoprotein class has a relatively fixed composition with respect to TC and Tgs, and since the 2 largest (chylomicrons and VLDL) refract light and cause plasma turbidity, hyperlipoproteinemia can be defined by observing a standing plasma sample, after 24 h storage at 4° C, followed by a more precise TC and Tg assay. Electrophoresis usually is *not* required to convert hyperlipidemia into HLP.

Defining the lipoprotein pattern does not conclude the diagnostic process, since no HLP can be regarded as unique. Each may be *secondary* to other disorders that must be ruled out (eg, hypothyroidism, alcoholism, renal disease) or may be *primary* (usually familial), in which case screening should be done to identify other family members (often asymptomatic) with HLP.

In evaluating lipid or lipoprotein measurements, one must be aware of the following: (1) Lipid and lipoprotein concentrations increase with age. A value acceptable for a middle-aged adult might be alarmingly high in a child of 10. (2) Because chylomicrons normally appear in the blood 2 to 10 h after a meal, a fasting specimen (12 to 16 h) should be used. (3) Lipoprotein concentrations are under dynamic metabolic control and are readily affected by diet, illness, drugs, and weight change. Lipid analysis should be done during a steady state. If abnormal, at least 2 more samples should be tested before selecting therapy (*diet is always step 1*). (4) When HLP is secondary to another disorder, its treatment usually will correct the HLP.

TYPE I HYPERLIPOPROTEINEMIA (HLP)

(Exogenous Hypertriglyceridemia; Familial Fat-Induced Lipemia; Hyperchylomicronemia)

A relatively rare congenital deficiency of either lipoprotein lipase activity or the lipase-activating protein apolipoprotein C-II. In either case the ability to remove or "clear" chylomicrons from the blood is impaired.

Symptoms, Signs, and Diagnosis

This disease is manifested in children or young adults by pancreatitis-like abdominal pains; pinkish-yellow papular cutaneous deposits of fat (eruptive xanthomas), especially over pressure points and extensor surfaces; lipemia retinalis; and hepatosplenomegaly. Symptoms and signs are exacerbated by increased dietary fat that accumulates in the circulation as chylomicrons.

Diagnosis: Spectacular plasma Tg levels cause marked lactescence. Chylomicrons, which refract light and produce lactescence, accumulate as a floating cream layer on standing overnight in the refrigerator. This cream layer overlying an otherwise clear plasma is often diagnostic, as is the failure of the lipoprotein lipase activity to increase after injection of IV heparin (post-heparin lipolytic activity).

TABLE 83–3. CHARACTERISTICS OF THE PRIMARY HYPERLIPOPROTEINEMIAS

Type	Other Names	Genetic Form	Plasma Cholesterol Level	Plasma Triglyceride Level	Risk for Atherosclerosis	Major Secondary Causes	Clinical Presentation	Treatment
I	Exogenous hypertriglyceridemia Familial hypertriglyceridemia Familial chylomicronemia Fat-induced hyperlipidemia Hyperchylomicronemia	Autosomal recessive; rare	Normal or slightly increased	Very greatly increased	Risk not increased	SLE; dysgammaglobulinemia; insulinopenic diabetes mellitus	Pancreatitis Eruptive xanthomas Hepatosplenomegaly Lipemia retinalis	Dietary: low intake of fat; no alcohol
II	Familial hypercholesterolemia Familial hyperbetalipoproteinemia Familial hypercholesterolemic xanthomatosis	Autosomal dominant; common	Greatly increased	(a) Normal (b) Slightly increased	Very strong risk, especially for coronary atherosclerosis	Excess dietary cholesterol; hypothyroidism; nephrosis; multiple myeloma; porphyria; obstructive liver disease	Accelerated atherosclerosis Xanthelasma Tendon and tuberous xanthomas Juvenile corneal arcus	Dietary: low-cholesterol, low-fat diet Drugs: cholestyramine, colestipol, niacin, lovastatin, probucol Possible surgery
III	Broad beta disease Familial dysbetalipoproteinemia Floating betalipoproteinemia	Mode of inheritance unclear; uncommon but not rare	Greatly increased	Greatly increased	Very strong risk for atherosclerosis, especially in peripheral and coronary arteries	Dysgammaglobulinemia; hypothyroidism	Accelerated atherosclerosis of coronary and peripheral vessels Planar xanthomas Tuberuptive and tendon xanthomas	Dietary: reduction to ideal weight; maintenance of low-cholesterol, balanced diet Drugs: niacin, clofibrate, gemfibrozil
IV	Endogenous hypertriglyceridemia Familial hyperprebetalipoproteinemia Carbohydrate-induced triglyceridemia	Common, often sporadic when familial; genetically heterogeneous	Normal or slightly increased	Greatly increased	Possible risk, especially for coronary atherosclerosis	Excess alcohol consumption; oral contraceptives; glycogen storage disease; pregnancy; nephrotic syndrome; stress	Possible accelerated atherosclerosis Glucose intolerance Hyperuricemia	Weight reduction; low-carbohydrate diet; no alcohol Drugs: niacin, gemfibrozil
V	Mixed hypertriglyceridemia Combined exogenous and endogenous hypertriglyceridemia Mixed hyperlipemia	Uncommon but not rare; genetically heterogeneous	Normal or slightly increased	Very greatly increased	Risk of atherosclerosis not clearly increased	Alcoholism; insulin-dependent diabetes mellitus; nephrosis; dysgammaglobulinemia	Pancreatitis Eruptive xanthomas Hepatosplenomegaly Sensory neuropathy Lipemia retinalis Hyperuricemia Glucose intolerance	Weight reduction; low-fat diet; no alcohol Drugs: niacin, gemfibrozil

Prognosis

Pancreatitis is the principal sequela. Abdominal pain that recurs during periods of fat indulgence may be marked by severe and sometimes fatal hemorrhagic pancreatitis. Avoidance of dietary fat prevents serious sequelae and allows for an otherwise normal life. There is no evidence that type I HLP predisposes to atherosclerosis.

Treatment

The goal is to reduce circulating chylomicrons to avoid episodes of acute pancreatitis. Since hypertriglyceridemia is promoted by ingesting fat, whether saturated, unsaturated, or polyunsaturated, a diet markedly restricted in *all* common sources of fat is effective. Calories can be supplemented and palatability enhanced by using 20 to 40 gm of medium chain (C_{12} or less) Tgs a day. These fatty acids are not transported via chylomicron formation, but are bound to albumin and pass directly through the portal system to the liver.

TYPE II HYPERLIPOPROTEINEMIA (HLP)

(Familial Hypercholesterolemia; Hyperbetalipoproteinemia; Familial Hypercholesterolemic Xanthomatosis)

A genetic disorder of lipid metabolism characterized by elevated serum TC in association with xanthelasma, tendon and tuberous xanthomas, arcus juvenilis, accelerated atherosclerosis, and early death from myocardial infarction (MI). This disorder occurs most often in a familial pattern of a dominant gene with complete penetrance and is much more severe in homozygotes than in heterozygotes. It appears to be caused by absent or defective LDL cell receptors, resulting in delayed LDL clearance, increased levels of plasma LDL_1, and accumulation of LDL cholesterol over joints, pressure points, and in blood vessels.

Symptoms, Signs, and Diagnosis

The patient may be asymptomatic, or any of the aforementioned manifestations may be present. Xanthomas are usually in the Achilles, patellar, and digital extensor tendons. A family history of premature CAD (before age 55) may be present.

The plasma TC elevation in the presumed heterozygote may be as much as 2 to 3 times normal, all secondary to increased LDL. The plasma is usually translucent, since LDL does not refract light, regardless of its concentration, and Tg levels are normal or slightly increased. In the rare presumed homozygote with this disorder, TC levels of 500 to 1200 mg/dL occur and are usually associated with xanthomas before age 10 yr. A normal free cholesterol:cholesterol ester ratio and phospholipid level differentiate this disorder from the marked hypercholesterolemia (with clear plasma) seen in obstructive liver disease (see below and under CHOLESTASIS in Ch. 65).

Prognosis

The incidence of xanthomas and other external stigmas will increase with each decade in the presumed heterozygote with this disorder. Sometimes, especially in females, an Achilles tendinitis will recur. Atherosclerosis, especially of the coronary vessels, is markedly accelerated, particularly in males. Of type II men, 1 in 6 will have a heart attack by age 40, and 2 in 3 by age 60. Homozygotes may develop and succumb to CAD and its sequelae before age 20.

Treatment

With lowered cholesterol, unsightly xanthomas will cease growing and regress or disappear. However, the major reason for therapy is to decelerate premature development of atherosclerosis and lessen the likelihood of CAD and MI. **For mild or moderate elevations of LDL cholesterol**, an altered diet is usually sufficient and represents step 1 in treatment. Dietary changes usually should be tried for at least 6 mo before determining that a drug is also needed. **For severe hypercholesterolemia** (eg, TC > 240 mg/dL, LDL > 160 mg/dL) **or familial disease,** it is appropriate to add a drug sooner. (See specific discussions below.)

Probucol 500 mg orally bid may lower LDL levels 10 to 15% when added to diet, but it often has the additional undesirable side effect of lowering HDL levels. Thyroid analogs like **D-thyroxine** effectively lower LDL levels but are contraindicated in patients with suspected or proven heart disease. **Clofibrate** has little effect on plasma TC or LDL levels in this disorder, may produce gallstones and other metabolic problems, and usually is not indicated. Other agents are generally less effective than strict dietary management.

Familial combined hypercholesterolemia is an apparently less common genetic cause of hypercholesterolemia that is sometimes confused with familial hypercholesterolemia. It is transmitted in a dominant manner but is often not chemically manifest until after adolescence. It appears to be due to excessive hepatic production of apolipoprotein B. Since apolipoprotein B is the major protein of VLDL and LDL, this disorder can lead to excess LDL, VLDL, or both, dependent upon clearance. One often finds different lipoprotein patterns in different affected members of the same family. Xanthomas are very uncommon in familial combined hypercholesterolemia, but there is a marked predilection to premature CAD. Dependent on the lipoprotein excess present, the disorder responds well to weight reduction, restriction of saturated fat and cholesterol, and followed when necessary by niacin 3 gm/day, lovastatin 20 to 40 mg/day, or a combination of cholestyramine with niacin or gemfibrozil.

Polygenic hypercholesterolemia is probably a heterogeneous group of disorders and accounts for the largest number of patients with genetic elevation of LDL. Some of these patients possess an abnormal LDL that binds poorly to receptors, resulting in retarded clearance of LDL from plasma. However, most patients with polygenic hypercholesterolemia exhibit impaired clearance of LDL for other reasons. Some are sensitive to dietary restriction of saturated fat and cholesterol. When this fails, therapy with lovastatin, cholestyramine, or niacin will usually totally reduce the elevated LDL to normal levels.

Secondary Hypercholesterolemia

Hypercholesterolemia is common in **biliary cirrhosis**, as is a marked increase in the serum phospholipids and an elevated free cholesterol:cholesterol ester ratio (> 0.2). The plasma is not lactescent because the overabundant lipoproteins (lipoprotein-x) are small and do not scatter light. Planar xanthomas and xanthelasma are common with prolonged and severe lipemia.

Hypercholesterolemia due to increased concentrations of LDL may be associated with **endocrinopathies** (hypothyroidism, hypopituitarism, diabetes mellitus) and usually is reversed by hormone therapy. Hypoproteinemias as in the **nephrotic syndrome**, metabolic aberrations such as **acute porphyria**, or **dietary excesses** with cholesterol-rich foods may also produce hyperbetalipoproteinemia. TC levels may be elevated secondary to increased concentrations of HDL in postmenopausal women or younger women taking oral contraceptives that primarily contain estrogen.

Type III Hyperlipoproteinemia (HLP)

(Broad Beta Disease; Dysbetalipoproteinemia)

A less common familial disorder characterized by the accumulation in plasma of a β-migrating VLDL, rich in Tgs and TC, associated with tuboeruptive and pathognomonic planar (palmar) xanthomas and a marked predisposition to severe premature atherosclerosis. It is often associated with abnormalities of apolipoprotein E and defective conversion and removal of VLDL from the plasma. Though usually familial, this type of HLP may be seen in dysproteinemias and hypothyroidism.

Symptoms, Signs, and Diagnosis

The disorder usually appears in early adulthood in men and 10 to 15 yr later in women. Peripheral vascular disease manifested by claudication or tuboeruptive xanthomas on the elbows and knees may be the first manifestations.

Plasma may be cloudy to grossly turbid, often with a slight chylomicron layer. Both TC and Tg levels are elevated, often equally. Precise definition of this abnormality requires ultracentrifugation and electrophoresis with the demonstration of a cholesterol-rich, β-migrating VLDL. A mild abnormality in glucose tolerance and hyperuricemia may be present.

Prognosis and Treatment

There is a marked predilection for early and severe CAD and peripheral arterial disease. With treatment, hyperlipidemia can nearly always be reduced to normal and the peripheral vessel disease may abate.

Weight reduction to ideal body weight and dietary restriction of cholesterol, saturated fat, and carbohydrate may suffice to reduce both TC and Tg levels and result in marked regression of xanthomas. For those who do not respond adequately, addition of niacin 2 to 3 gm/day orally, gemfibrozil 1.2 gm/day orally, or clofibrate 2 gm/day orally is most effective and usually reduces blood lipid to normal levels. Lovastatin has also been reported to be effective in many patients with type III HPL.

Type IV Hyperlipoproteinemia (HLP)

(Endogenous Hypertriglyceridemia; Hyperprebetalipoproteinemia)

A common disorder, often with a familial distribution, characterized by variable elevations of plasma Tgs, contained predominantly in very low-density (pre-β) lipoproteins, and a possible predisposition to atherosclerosis. Depending on the level of endogenous Tg used to define type IV HLP, the disorder is common in adult American middle-aged men.

Symptoms, Signs, and Diagnosis

This lipidemia is frequently associated with mildly abnormal glucose tolerance curves and obesity, and may be exaggerated when dietary fat is restricted and carbohydrate added reciprocally (with caloric intake kept constant). Plasma is turbid and Tg levels disproportionately elevated. TC may be normal or slightly increased (frequently secondary to stress, alcoholism, and dietary indiscretion) and may be associated with hyperuricemia.

Prognosis and Treatment

The prognosis is uncertain. The disorder may be associated with premature CAD.

Weight reduction, when applicable, is the most effective treatment and will often reduce the blood lipid to normal levels. Maintenance of proper body weight and dietary restriction of carbohydrate and alcohol are important. Niacin 3 gm/day orally or gemfibrozil 0.6 to 1.2 gm/day orally in divided doses will further reduce the lipidemia in those not controlled by diet.

Type V Hyperlipoproteinemia (HLP)

(Mixed Hypertriglyceridemia; Mixed Hyperlipidemia; Hyperprebetalipoproteinemia with Chylomicronemia)

An uncommon disorder, sometimes familial, associated with defective clearance of exogenous and endogenous Tgs and the risk of life-threatening pancreatitis.

Symptoms, Signs, and Diagnosis

This disorder usually first appears in early adulthood with showers of eruptive xanthomas over the extensor surfaces of the extremities, lipemia retinalis, hepatosplenomegaly, and abdominal pain. Symptoms are exacerbated by increased ingestion of dietary fats. Plasma Tg levels usually are markedly elevated with only modest rises in TC. Plasma is turbid to cloudy with a distinct cream layer on top. Levels of lipoprotein lipase are usually normal. Hyperuricemia, glucose intolerance, and obesity are common. This pattern may be secondary to alcoholism, nephrosis, starvation with refeeding, or severe insulinopenic diabetes.

with HLA types A3 and A28. The pattern of inheritance is not clear, but some kinships appear to have an autosomal recessive pattern.

In type II, glandular failure generally occurs in adults, with peak incidence at age 30. It always involves the adrenal cortex and frequently also the thyroid gland **(Schmidt's syndrome)** and the pancreatic islets, producing insulin-dependent diabetes mellitus **(IDDM)**. Antibodies against the target organs are frequently present, but their role in producing glandular damage is unclear. Some patients have thyroid-stimulating antibodies and initially present with the clinical picture of hyperthyroidism. The glandular destruction seen in these patients is chiefly a result of cell-mediated autoimmunity, probably because of depressed suppressor T-cell function. In addition, reduced cell-mediated immunity is frequently present, manifested by poor response on skin testing to standard antigens such as *Candida, Trichophyton,* and tuberculin. Depressed reactivity is also found in about 30% of first-degree relatives with normal endocrine function. There is a characteristic HLA pattern, and it has been suggested that the specific HLA types in type II are associated with susceptibility to certain viruses that induce the destructive reaction.

An additional group, **type III,** occurs in adults and does not involve the adrenal cortex, but includes at least 2 of the following: thyroid deficiency, IDDM, pernicious anemia, vitiligo, and alopecia. Since the diagnosis of the type III pattern depends on the absence of adrenocortical insufficiency, it may merely be a wastebasket of combined disease that is converted to type II if adrenal failure develops.

Symptoms, Signs, and Diagnosis

The clinical appearance of patients with polyglandular deficiency syndromes is the sum of the picture of each of the individual deficiencies. There is no specific sequence for appearance of individual glandular damage. Measurement of the levels of circulating antibody against the endocrine organs or their components does not appear to be useful, since such antibodies may persist for years without development of clinical endocrine failure. However, the presence of antibodies is clearly helpful in differentiating autoimmune from tuberculous hypoadrenalism and determining the cause of hypothyroidism. The presence of multiple endocrine deficiencies may raise a question of hypothalamic-pituitary failure. In almost all instances, elevated plasma levels of pituitary tropic hormones will demonstrate the peripheral nature of the defect; but rare instances of hypothalamic-pituitary insufficiency have also been reported as a part of the type II syndrome (see Ch. 85).

Treatment

Treatment of the various glandular deficiencies is the same as for sporadic examples of the individual diseases discussed elsewhere in THE MANUAL, but the interaction of multiple deficiencies (eg, adrenal cortical insufficiency combined with diabetes mellitus) may complicate clinical management. Patients manifesting hypofunction of one organ should be observed during follow-up over a period of years for development of additional defects. Gonadal failure does not respond, and chronic mucocutaneous candidiasis is usually resistant to treatment.

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91. DISORDERS OF CARBOHYDRATE METABOLISM

DIABETES MELLITUS (DM)

(See also DIABETES MELLITUS in Ch. 181)

*A syndrome characterized by hyperglycemia resulting from impaired insulin secretion and/or effectiveness, associated with risks for diabetic ketoacidosis **(DKA)** or nonketotic hyperglycemic-hyperosmolar coma **(NKHHC)** and a group of late complications including retinopathy, nephropathy, atherosclerotic coronary and peripheral arterial disease, and peripheral and autonomic neuropathies.* DM has diverse genetic, environmental, and pathogenic origins.

Classification and Pathogenesis

Current classifications are based on clinical criteria, eg, the presence or absence of a propensity to DKA, as well as on ancillary criteria used to segregate specific pathogenic forms of DM (see TABLE 91–1).

Insulin-dependent diabetes mellitus (IDDM, type I DM) accounts for 10 to 15% of all cases of DM and is clinically characterized by hyperglycemia and a propensity to DKA. Its control requires chronic insulin treatment. Although it may occur at any age, it most commonly develops in childhood or adolescence and is the predominant type of DM diagnosed before age 30. The term IDDM (or type I DM) is also used more restrictively to refer to the subset of patients with DKA-prone DM diagnosed prior to age 30, in which specific HLA phenotypes are associated with detectable serum islet cell cytoplasmic antibodies **(ICA)** and/or islet cell surface antibodies **(ICSA)** in about 80% of cases at diagnosis. In these patients, IDDM results from a genetically conditioned, immune-mediated, selective destruction of > 90% of their insulin-secreting β cells. If these patients die shortly after the onset of IDDM, their pancreatic islets exhibit **insulitis**, which is characterized by an infiltration of T lymphocytes accompanied by macrophages and B lymphocytes and by the loss of most of the β cells, without involvement

TABLE 91–1. GENERAL CHARACTERISTICS OF THE MAJOR CLINICAL TYPES OF DIABETES MELLITUS (DM)

Characteristic	*Insulin-Dependent DM (IDDM, Type I DM)*	*Non–insulin-Dependent DM (NIDDM, Type II DM)*
Age at onset	Most commonly < 30 yr	Most commonly > 30 yr
Associated obesity	No	Very common
Propensity to ketoacidosis requiring insulin treatment for its control	Yes	No
Endogenous insulin secretion	Extremely low to undetectable plasma insulin and C-peptide levels	Significant but variable levels of insulin secretion that are low relative to plasma glucose levels and accompanied by insulin resistance
Twin concurrence	< 50%	> 90%
Associated with specific HLA-D antigens	Yes	No
Islet cell antibodies at diagnosis	Yes	No
Islet pathology	Insulitis, selective loss of most β cells	Smaller, normal-appearing islets; amyloid (amylin) deposition common
Associated risks for retinopathy, nephropathy, neuropathy, and atherosclerotic coronary and peripheral vascular disease in most Western populations	Yes	Yes
Hyperglycemia responds to sulfonylureas	No	Yes, initially in many patients

of the glucagon-secreting α cells. Cell-mediated immune mechanisms are believed to play the major role in the β-cell destruction.

The ICA and ICSA present at diagnosis usually become undetectable after 1 to 2 yr; they may be primarily a response to β-cell destruction, but some are cytotoxic for β cells and may contribute to their loss. Cytotoxicity is particularly associated with islet cell autoantibodies that selectively bind to β cells (many ICA are not β cell specific). Glutamic acid decarboxylase **(GAD)** was recently found to be the autoantigen for one of the β cell–specific autoantibodies present at diagnosis in ~80% of IDDM patients. (GAD, the enzyme that synthesizes the neurotransmitter γ-aminobutyric acid, is found in high levels only in pancreatic islet β cells and in the brain.) The clinical onset of IDDM is characteristically abrupt, but it may occur in some patients years after the insidious onset of the underlying autoimmune process. (Detectable ICA and subclinical alterations in glucose tolerance have been found in some siblings and parents of IDDM patients, years before these first-degree relatives developed IDDM.)

In white populations there is a strong association between IDDM diagnosed before age 30 and specific HLA-D phenotypes (HLA-DR3, HLA-DR4, and HLA-DR3/HLA-DR4), and one or more genes that convey susceptibility to IDDM are believed to be located near or in the HLA-D locus on chromosome 6. Specific HLA-DQ alleles appear to be more intimately related to risks for or protection from IDDM than HLA-D antigens, and current evidence suggests that genetic susceptibility to IDDM is probably polygenic. Only 10 to 12% of newly diagnosed children with IDDM have a first-degree relative with IDDM. The concordance rate for IDDM in monozygotic twins is ≤ 50%, and in genetically susceptible individuals some environmental factor, probably a virus (congenital rubella, mumps, and coxsackie B viruses have been postulated), appears to incite the development of autoimmune β-cell destruction and IDDM.

Non–insulin-dependent diabetes mellitus (NIDDM, type II DM) is characterized clinically by hyperglycemia that is not associated with a propensity to DKA, but some patients intermittently or persistently require insulin to control or prevent symptomatic degrees of hyperglycemia, which might lead to NKHHC. NIDDM is usually the type diagnosed in patients > 30 yr of age, but it also occurs in children and adolescents. It is commonly associated with obesity. The concordance rate for NIDDM in monozygotic twins is > 90%, and genetic factors appear to be the major determinants of its development. No association between NIDDM and specific HLA phenotypes or ICA has been demonstrated (an exception is a subset of nonobese adults with detectable ICA who carry one of the HLA phenotypes and who may eventually develop IDDM). The pancreatic islets in NIDDM retain β cells in ratios to α cells that are not consistently altered, and normal β-cell mass appears to be preserved in most patients. Pancreatic islet amyloid, resulting from a deposition of amylin, is found in a high percentage of NIDDM patients at autopsy, but its relationship to the pathogenesis of NIDDM is unknown.

NIDDM is a heterogeneous group of disorders in which hyperglycemia results from both an impaired insulin secretory response to glucose and decreased insulin effectiveness (**insulin resistance**). Most patients retain a significant, but variable, insulin secretory capacity but exhibit a decreased insulin secretory response to glucose, which is most pronounced in patients with both fasting and postprandial hyperglycemia. Recent studies using an assay that is highly specific for insulin have demonstrated that there is a considerable overlap in fasting plasma insulin levels in NIDDM patients and age- and weight-matched controls, but that both obese and nonobese NIDDM patients have a delayed and *decreased* rise in plasma insulin following glucose ingestion despite their higher plasma glucose levels. The degree of abnormality in the peripheral plasma insulin response to glucose ingestion in both obese and nonobese NIDDM patients correlates with the degree of fasting hyperglycemia.

Persistent hyperglycemia has a "toxic" effect on β cells, which may augment the primary abnormality in insulin secretion and explain why many NIDDM patients show some

improvement in the insulin secretory response to ingested glucose after a period of vigorous insulin control of the hyperglycemia or aggressive diet therapy. Some primary β-cell abnormality may be necessary for the development of NIDDM, but an acquired (eg, obesity related) or genetically determined insulin resistance appears to be required. NIDDM patients exhibit decreased insulin effectiveness in restraining hepatic glucose output and in stimulating glucose uptake by skeletal muscle, which are important in normal plasma glucose regulation. Obesity and inadequate insulin secretion can cause similar manifestations of insulin resistance, and the existence of a primary genetically determined insulin resistance in most NIDDM patients is controversial. The insulin resistance does not appear to result from genetic alterations in insulin receptor numbers or function, but a role for genetically determined postreceptor defects is possible. In obese NIDDM patients, improvement in the insulin secretory response to glucose is frequently observed after a period of weight reduction associated with decreased hyperglycemia or after rigorous insulin treatment.

Insulinopathies: Rare cases of DM, with the clinical characteristics of NIDDM, result from the heterozygous inheritance of a defective gene, leading to secretion of insulin that does not bind normally to the insulin receptor. These patients have greatly elevated plasma immunoreactive insulin **(IRI)** levels associated with normal plasma glucose responses to exogenous insulin.

Maturity-onset diabetes of young people (MODY) is NIDDM with an autosomal dominant inheritance found in successive generations of some families, frequently in asymptomatic, nonobese, young adolescents.

Diabetes attributed to pancreatic disease: Chronic pancreatitis, particularly in alcoholics, is frequently associated with diabetes. In Asia, Africa, and the Caribbean, malnutrition-related DM is commonly observed in young, severely emaciated patients with severe protein deficiency and pancreatic disease, who are not DKA-prone but who may require insulin treatment.

Diabetes associated with other endocrine diseases: DM can be a secondary manifestation of Cushing's syndrome, acromegaly, pheochromocytoma, glucagonoma, primary aldosteronism, or somatostatinoma, resulting from the influence of the primary endocrine abnormality on insulin effectiveness and/or secretion. Patients with certain autoimmune endocrine diseases, eg, Graves' disease, Hashimoto's thyroiditis, and idiopathic Addison's disease, have an increased prevalence of IDDM (see Ch. 90).

Insulin-resistant DM associated with acanthosis nigricans (type A and type B insulin resistance syndromes): Two rare syndromes result from marked insulin resistance at the insulin receptor level associated with acanthosis nigricans. Type A results from genetic alterations in the insulin receptor. Type B results from circulating antibodies to the insulin receptor and may be associated with other evidence of autoimmune disease.

Lipoatrophic diabetes, a rare syndrome in which insulin-resistant DM is associated with an extensive symmetrical or virtually complete disappearance of subcutaneous adipose tissue, has been linked to genetic alterations in the insulin receptor.

Diabetes induced by β-cell toxins: Vacor™, a rodenticide commonly used in suicide attempts in Korea, is cytotoxic for human islets and commonly causes IDDM in survivors. The use of streptozocin in treating pancreatic islet carcinomas rarely causes diabetes, although this β-cell toxin can induce experimental diabetes in rats.

Symptoms and Signs

DM has diverse initial presentations. IDDM patients usually present with symptomatic hyperglycemia or DKA. NIDDM may initially present with symptomatic hyperglycemia or NKHHC, but is frequently diagnosed in asymptomatic patients during a routine medical study or when patients present with clinical manifestations of a late complication.

Symptomatic hyperglycemia: Polyuria, polydipsia, and weight loss, despite a normal or sometimes increased dietary intake, occur when elevated plasma glucose levels cause

marked glucosuria and an osmotic diuresis, resulting in dehydration. Polyuria is the initial manifestation. In IDDM there also is usually a rise in plasma ketones, frequently followed by DKA, sometimes within hours. In NIDDM symptomatic hyperglycemia may persist for days or weeks before medical attention is sought; in women it is frequently associated with itching due to vaginal candidiasis.

Acute complications: see below under Diagnosis and Treatment of Diabetic Ketoacidosis (DKA); and Diagnosis and Treatment of Nonketotic Hyperglycemic-Hyperosmolar Coma (NKHHC).

Late complications: The risks of a late clinical complication vary markedly in individuals but generally increase with increasing duration of DM. Hyperglycemia causes the initial metabolic alterations and early functional alterations in the kidney, peripheral nerves, and retina in diabetics; but evidence suggests that once these structural alterations reach a given stage, factors other than hyperglycemia determine the subsequent course. The symptoms and signs of late complications of DM mimic those of pathologically similar or indistinguishable disease in the same organ or system in nondiabetics. These manifestations may be present at diagnosis in those with NIDDM, but not in those with IDDM.

Atherosclerotic coronary artery disease (manifested by angina and/or myocardial infarction) and peripheral atherosclerotic vascular disease (manifested by intermittent claudication and gangrene) are more common in diabetics than in nondiabetics and occur at an earlier age.

Diabetic retinopathy (see also DIABETIC RETINOPATHY in Ch. 226): Background retinopathy (the initial retinal changes seen on ophthalmoscopic examination or in retinal photographs) does not significantly alter vision, but it can lead to processes that cause blindness (eg, macular edema or proliferative retinopathy with retinal detachment or hemorrhage). *Patients with background retinopathy require regularly scheduled examinations by an ophthalmologist, since specific retinal findings are indications for prompt retinal laser photocoagulation therapy to prevent or control macular edema or proliferative retinopathy.* Evidence of retinopathy, rarely present at diagnosis in IDDM, is present in up to 20% of NIDDM patients at diagnosis. About 85% of all diabetics eventually develop some degree of retinopathy.

Diabetic nephropathy is usually asymptomatic until end-stage renal disease develops, but it can cause the nephrotic syndrome prior to the development of uremia. Nephropathy develops in 30 to 50% of IDDM patients and in a smaller percentage of NIDDM patients. In patients with IDDM, persistent clinically detectable albuminuria (≥ 300 mg/L) unexplained by other urinary tract disease can predict a progressive decrease in GFR and the development of end-stage renal disease within 3 to 20 yr (median, 10 yr). Albuminuria is absent during the first 5 yr of IDDM; its incidence increases and peaks during the 2nd decade and then declines. In NIDDM albuminuria is occasionally present at diagnosis. Albuminuria is almost 2.5 times higher in IDDM patients with diastolic BP > 90 mm Hg than in those in whom it is < 70 mm Hg. Whether the higher BPs result from more advanced renal disease or whether clinical nephropathy develops primarily in patients with a predisposition to essential hypertension is controversial, but hypertension accelerates the progression to end-stage renal disease.

Diabetic neuropathy: The most common form is a distal, symmetric, predominantly sensory **polyneuropathy** that causes sensory deficits with a stocking-glove distribution, which begin and are usually most marked in the feet and legs. Diabetic polyneuropathy is frequently asymptomatic but may be associated with numbness, tingling, and paresthesias in the extremities, and less often with debilitating, severe, deep-seated pain and hyperesthesias. Ankle jerks are usually decreased or absent. Symptoms and signs of polyneuropathy can be present at diagnosis in patients with NIDDM but are not usually found in those with recently diagnosed IDDM. Other causes of polyneuropathy must be excluded (see Ch. 131). Acute, painful **mononeuropathies** affecting the 3rd, 4th, or 6th cranial nerve, which may spontaneously improve over a period of weeks to months, occur more frequently in older diabetics and are attributed to nerve infarctions. **Autonomic neuropathy** occurs primarily in diabetics with polyneuropathy and can cause postural hypotension, disordered sweating, impotence and retrograde ejaculation in men, impaired bladder functions, delayed gastric emptying, esophageal dysfunction, constipation or diarrhea, and nocturnal diarrhea. Alterations in the cardiac rate response to the Valsalva maneuver or on standing and in heart rate variation during deep breathing are evidence of autonomic neuropathy in diabetics.

Foot ulcers are an important cause of morbidity in DM. The major predisposing cause is diabetic polyneuropathy—the sensory denervation impairs the perception of trauma from common causes (ill-fitting shoes, pebbles, etc), and alterations in proprioception lead to an abnormal pattern of weightbearing and in some instances to the development of typical **Charcot's joints.**

Infections commonly result from manipulation of an ingrown toenail, plantar corn, or callus. A mycotic infection may be the initial process, leading to wet interdigital lesions, cracks, fissures, and ulcerations that favor secondary bacterial invasion. Patients with infected foot ulcers frequently feel no pain because of neuropathy and have no systemic symptoms until late in a neglected course. The infection may extend into the deeper soft tissues and result in osteomyelitis of foot bones. Cultures of samples from superficial and deep tissues usually demonstrate mixed bacterial flora, including aerobic gram-positive cocci and gram-negative enteric bacteria and anaerobic organisms, particularly *Bacteroides* sp and various anaerobic gram-positive cocci; differences in the specific components of the flora at the 2 sites are common. Deep ulcers and particularly those associated with any detectable cellulitis require immediate hospitalization, since there are risks of developing systemic toxicity and permanent disability, and early surgical debridement is an essential part of appropriate management.

Diagnosis

The principal aim of diagnosis is to identify patients at risk for symptomatic hyperglycemia, for DKA or NKHHC, and for late clinical complications, ruling out those who have fluctuations only in the upper range of their plasma glucose levels, which may not convey the risks associated with DM. Symptomatic hyperglycemia, DKA, or NKHHC unequivocally establishes a diagnosis of DM. In asymptomatic patients, DM is established when the diagnostic criteria for fasting hyperglycemia recommended by the National Diabetes Data Group **(NDDG)** are met: a plasma (or serum) glucose level of ≥ 140 mg/dL after an overnight fast on 2 occasions in an adult or child (the glucose concentration in venous samples of whole blood is about 15% lower than that in plasma). If these criteria are met, an **oral glucose tolerance test (OGTT**—see below) is unnecessary.

The major indication for an OGTT is to exclude or diagnose NIDDM in those suspected of having diabetes although fasting or symptomatic hyperglycemia is absent; eg, in patients with a clinical condition that might be related to undiagnosed DM (eg, polyneuropathy, retinopathy). However, an OGTT diagnosis of DM does not necessarily predict the subsequent development of fasting or symptomatic hyperglycemia. Various conditions (other than DM) and drugs can cause abnormalities in the OGTT. The NDDG criteria (see below and in TABLE 91–2) for an OGTT diagnosis of DM apply only to healthy patients who do not have infections, acute cardiovascular or cerebrovascular disease, endocrine disease that impairs glucose tolerance, or hepatic, renal, or CNS disease. These criteria also do not apply to patients treated with drugs that can impair glucose tolerance (eg, thiazides, phenytoin, glucocorticoids, indomethacin, nicotinic acid, oral contraceptives containing synthetic estrogens) or to patients who develop nausea, sweating, faintness, or pallor during the test. (The effects of **pregnancy** on the OGTT and the diagnosis of gestational diabetes are discussed under DIABETES MELLITUS in Ch. 181.)

No special dietary preparation is required for an OGTT unless the patient has been ingesting < 150 gm/day of carbohydrate. The test should be done in the morning after a 10- to 14-h fast, without prior coffee or smoking, with the patient seated upright. A chilled

TABLE 91–2. DIAGNOSTIC CRITERIA OF THE NATIONAL DIABETES DATA GROUP

	Criteria for Diagnosis of Diabetes Mellitus and Impaired Glucose Tolerance (All plasma glucose values in mg/dL)						*Criteria for Diagnosis of Gestational Diabetes* (100 gm OGTT)
	Normal		*Diabetes Mellitus*		*Impaired Glucose Tolerance*		*Venous Plasma Glucose*
	Adult	Child	Adult	Child	Adult	Child	
FPG	< 115	< 130	≥ 140	≥ 140	115–139	130–139	Fasting ≥ 105 mg/dL
OGTT	< 140	< 140	≥ 200	≥ 200	140–199	140–199	1 h ≥ 190 mg/dL 2 h ≥ 165 mg/dL 3 h ≥ 145 mg/dL

FPG = fasting plasma glucose; OGTT = oral glucose tolerance test (at least 2 values).

From Harris M, et al for the National Diabetes Data Group: "Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance." *Diabetes* 28:1049, 1979. Copyright 1979 by American Diabetes Association, Inc.; reprinted with permission.

solution containing 75 gm of glucose is used in adults; the test dose in children is 1.75 gm/kg ideal body wt up to a maximum of 75 gm. Commercial solutions, flavored for palatability, may be used. Blood samples are obtained fasting and at 30-min intervals over 2 h from the initial swallow of the glucose solution. A diagnosis of DM in a nonpregnant adult is justified if the plasma glucose level at both 2 h and one other time between 0 and 2 h is ≥ 200 mg/dL. The criteria for the OGTT diagnosis in asymptomatic *children* are stricter (because of the greater risk of overdiagnosing DM) and also require a fasting plasma glucose ≥ 140 mg/dL. A final diagnosis of DM based solely on an OGTT requires a repeated positive test.

As indicated in TABLE 91–2, the NDDG also recommends criteria for the diagnosis of impaired glucose tolerance (IGT) in individuals who do not meet the OGTT diagnostic criteria for DM, but whose plasma glucose values are higher than normal. Patients with IGT may be at increased risk of developing fasting or symptomatic hyperglycemia, but in many patients the IGT does not progress or reverts to normal.

Treatment

General considerations: There is good evidence that hyperglycemia conveys risks for all of the common late complications of DM, which are the major causes of excess morbidity and mortality in diabetics. However, there is no generally applicable and consistently effective means of maintaining persistently *normal* plasma glucose fluctuations in diabetics, and efforts to do so entail significant risks of causing frequent or severe hypoglycemic episodes, particularly in IDDM patients. Treatment regimens differ in the priorities assigned to keeping the risks for hypoglycemia *minimal* and to keeping the diurnal plasma glucose fluctuations in a normal to near-normal range. Regimens are effective in preventing symptomatic hyperglycemia and DKA or NKHHC under most circumstances, but their ability to reduce the risks for the common late complications of DM is unknown.

The recommended target maximum acceptable plasma glucose levels vary, but postprandial plasma glucose levels > 200 mg/dL should be avoided whenever possible with minimal risk of hypoglycemia. This stems from the observation in the Pima Indian population, 40% of whom have NIDDM, that diabetic complications are rare in individuals whose 2-h plasma glucose level during an OGTT is < 200 mg/dL. Many authorities add the recommendation that fasting levels be kept ≤ 130 mg/dL. These goals are possible in most NIDDM patients and some IDDM patients, but they must be individualized and should be modified when circumstances make any risk of hypoglycemia unacceptable (eg, in patients with a short life expectancy, those with cerebrovascular or cardiac disease) or increase the risks of being hypoglycemic (eg, in patients who are unreliable or who have autonomic neuropathy).

Patient education is essential to ensure the effectiveness of the prescribed therapy, to recognize indications for seeking immediate medical attention, and to carry out appropriate foot care. On each physician visit, the patient should be assessed for symptoms or signs of complications, including a check of the feet and the pulses and sensation in the feet and legs, and a urine test for albumin. The BUN or serum creatinine levels should be assessed regularly (at least yearly), and an ECG and complete ophthalmologic evaluation should be performed at least yearly (see DIABETIC RETINOPATHY in Ch. 226). Coexistent hypertension or hypercholesterolemia increases the risks for specific late complications and requires special attention and appropriate treatment (see HYPERTENSION in Ch. 24 and ANOMALIES IN LIPID METABOLISM in Ch. 83). Psychologic problems are frequently seen in children and adolescents with IDDM and their families as a result of the associated stresses, and professional assistance is often helpful.

Because there is an increased risk of acute renal failure in diabetics, x-ray studies that require IV injection of contrast dyes should be performed only when absolutely necessary and only when the patient is well hydrated.

Although β-adrenergic blockers (eg, propranolol) can be used safely in most diabetics, they can mask the β-adrenergic symptoms of insulin-induced hypoglycemia and delay an appropriate patient response. In some insulin-treated patients, they can contribute to severe hypoglycemia by impairing the normal counterregulatory response.

In treating IDDM, chronic insulin therapy is always required, but the degree of hyperglycemia aimed for varies, as described below under Insulin Treatment Regimens. **Patients with NIDDM exhibit varying propensities to symptomatic hyperglycemia.** Many obese patients with NIDDM are seldom symptomatic, including some who intermittently or fairly persistently maintain plasma glucose levels around 300 mg/dL. For such patients, weight reduction alone is preferred, because it avoids the risks associated with insulin or an oral hypoglycemic agent. If improvement in hyperglycemia is not achieved by diet, some authorities institute insulin therapy; others prefer an initial trial with an oral hypoglycemic agent. Other NIDDM patients, usually obese, become symptomatic in association with infections, trauma, exposure to drugs that impair glucose tolerance, following binge eating and rapid weight gain, or for reasons that are not apparent. Insulin treatment is the most rapid and predictably effective means of correcting the hyperglycemia and avoiding the risk of NKHHC in such patients. Many physicians prefer to continue insulin treatment after recovery from such acute episodes, but this is a matter of clinical preference, for it is frequently possible to resume maintenance of the desired degree of hyperglycemia restriction with diet alone or with an added oral hypoglycemic agent. Finally, some (usually nonobese) NIDDM patients cannot be adequately controlled without insulin. Many physicians underestimate the risks associated with symptomatic hyperglycemia in NIDDM, because its progression to NKHHC is less predictable and usually less rapid than the progression of symptomatic hyperglycemia to DKA in IDDM, but NKHHC has a mortality rate of > 50%.

Plasma Glucose Monitoring

All patients should be instructed in self–glucose-monitoring, and insulin-treated patients should be taught to adjust their insulin dosages accordingly. A variety of commercial reagent strips are available for determining the glucose concentrations in a drop of fingertip blood; the results are determined by comparing the strip with a color chart provided by the manufacturer or by using a reflectance meter that provides a numeric read-out (glucose concentration in fingertip blood is equivalent to that in venous plasma). A spring-powered lancet is recommended to obtain the fingertip blood sample. The patient's testing technique should be evaluated at regular intervals. The frequency of testing is determined individually. IDDM patients usually monitor their plasma glucose fasting, 1 h after each meal, and

have a pattern of plasma glucose control that fluctuates erratically between marked hyperglycemia and frequent episodes of symptomatic hypoglycemia. Many of these patients improve when switched to a modified MSI regimen that provides most of the daily insulin as rapid-acting insulin in daily adjusted dosages before each meal, with some intermediate-acting insulin before the evening meal or at bedtime. The aim is not to maintain the diurnal plasma glucose fluctuations in a near-normal range, but to stabilize the fluctuations in a range that prevents symptomatic hyper- and hypoglycemia.

Brittle diabetes is most common in patients with no residual insulin secretory capacity, in whom insulin therapy is a crude and grossly inadequate substitute for a normal insulin secretory mechanism. The metabolic processes through which insulin affects the plasma levels of glucose, albumin-bound free fatty acids, and ketones are normally regulated by shifts in the balance between the effects of insulin and the opposing effects of glucagon (in liver) and the adrenergic autonomic nervous system. These **counterregulatory mechanisms** are independently regulated and normally increased during fasting, exercise, and other conditions that require protection against hypoglycemia (exercise increases skeletal muscle glucose uptake in a way that does not require insulin). Insulin doses must be adequate to deal with a sudden increase in counterregulatory mechanisms and to prevent rapidly developing symptomatic hyperglycemia and hyperketonemia, but this frequently produces transient plasma insulin excess. Counterregulatory responses to hypoglycemia become impaired in some chronic IDDM patients, limiting the patient's capacity to adapt to transient plasma insulin excesses.

Complications of Insulin Treatment

An insulin reaction (hypoglycemia) is an inherent risk that may occur because of an error in insulin dosage, a missed meal, unplanned exercise (patients are usually instructed to reduce their insulin dose or to increase their carbohydrate intake before planned exercise), or without apparent cause. (The symptoms and signs are discussed under HYPOGLYCEMIA, below.) Patients are taught to recognize symptoms of hypoglycemia, which usually respond rapidly to the ingestion of carbohydrate-containing fluids or foods. All diabetics should carry candy or lumps of sugar. An identification card, bracelet, or necklace indicating that the patient is an insulin-treated diabetic aids recognition of hypoglycemia in emergencies.

Local allergic reactions (at the site of insulin injections) are less common with purified porcine and human insulins. There is often immediate pain and burning, followed after several hours by local erythema, pruritus, and induration, the latter sometimes persisting for days. Most reactions spontaneously disappear after weeks of continued insulin injection and require no specific treatment, although antihistamines are sometimes used.

Generalized insulin allergy (usually to the insulin molecule) is rare but can occur when treatment is discontinued and restarted after a lapse of months or years. Such reactions may occur with any type of insulin, including human biosynthetic insulin. Symptoms usually develop shortly after an injection and may include urticaria, angioedema, pruritus, bronchospasm, and, in some instances, circulatory collapse. Treatment with antihistamines may suffice, but epinephrine and IV glucocorticoids are frequently required. *Insulin treatment should be stopped immediately.* If continued insulin treatment is required after the condition stabilizes, skin testing with a panel of purified insulin preparations (while hospitalized) and desensitization by a physician experienced in the management of this problem should be performed.

Immunologic insulin resistance: Most patients treated with insulin for 6 mo have antibodies to insulin. The relative antigenicity of purified insulin preparations is bovine > porcine > human (biosynthetic or semisynthetic), but genetic factors also affect individual response. Circulating insulin-binding antibodies can modify the pharmacokinetics of free insulin absorbed from a s.c. or IV injection, but in most patients they have no adverse effect on treatment. When resistance occurs, requirements are usually < 500 u./day, but some patients require > 1000 u./day. Increases in insulin to ≥ 200 u./day associated with marked increases in the plasma insulin-binding capacity indicate a diagnosis of immunologic insulin resistance. If the patient has been treated with bovine or mixed bovine-porcine preparations, switching to purified porcine or human insulin may lower the requirement. A concentrated preparation (U-500) of purified porcine, regular insulin is available. Remission may be spontaneous or may be induced in some NIDDM patients who can stop insulin treatment for 1 to 3 mo. Prednisone may decrease insulin requirements within 2 wk; treatment is usually initiated with about 30 mg bid and is tapered as the requirements decrease.

TABLE 91–4. CHARACTERISTICS OF SULFONYLUREA AGENTS

Generic Name	Daily Dosage Range (mg)	Duration of Action (h)	Tablet Size (mg)	Doses/day
Tolbutamide	500–3000	6–12	250, 500	2–3
Chlorpropamide	100–750	60	100, 250	1
Acetohexamide	250–1500	12–18	250, 500	1–2
Tolazamide	100–1000	12–24	100, 250, 500	1–2
Glyburide	2.5–20	Up to 24	1.25, 2.5, 5	1–2
Glipizide	5–40	Up to 24	5, 10	1–2

Modified from Melander A: "The clinical pharmacology of glipizide." *American Journal of Medicine* 75 (Suppl 5B):41–45, 1983; and from Skillman TG, Feldman JM: "The pharmacology of sulfonylureas." *American Journal of Medicine* 70:363, 1981; used with permission.

Local fat atrophy or hypertrophy at sites of s.c. insulin injection is relatively rare and usually improves by switching to human insulin and injecting it directly into the affected area. No specific treatment of local fat hypertrophy is required, but injection sites should be rotated in all patients because repeated insulin injections at the same site can induce local fat hypertrophy.

Oral Hypoglycemic Agents

Oral hypoglycemic agents are not used to treat IDDM because they cannot prevent symptomatic hyperglycemia or DKA in such patients. There are 2 classes of oral hypoglycemic agents—sulfonylureas and biguanides (eg, phenformin). **Biguanides** are not currently approved for treatment of NIDDM in the USA (phenformin was linked to an increased frequency of lactic acidosis). The **sulfonylureas** lower plasma glucose primarily by stimulating insulin secretion and also by enhancing insulin effects in some target tissues and inhibiting hepatic glucose synthesis. Sulfonylureas differ in potency and duration of action (see TABLE 91–4); they bind to plasma proteins by ionic and nonionic interactions. Tolbutamide, chlorpropamide, acetohexamide, and tolazamide bind ionically, and their durations of action can be altered by the administration of drugs that can displace them (phenylbutazone, salicylates, sulfonamides). All of the sulfonylureas are metabolized in the liver, but only tolbutamide and tolazamide are inactivated exclusively by the liver. About 30% of chlorpropamide is normally disposed of by urinary excretion, and the principal hepatic metabolite of acetohexamide is highly active and excreted in urine; both drugs carry an increased risk of hypoglycemia in patients with impaired renal function.

Authorities differ in the extent to which they recommend sulfonylureas. Some prefer to use insulin whenever any treatment for hyperglycemia in addition to weight reduction is indicated in an NIDDM patient. They note that the sulfonylureas do not provide a rapid and consistently effective means of treating or preventing *symptomatic* hyperglycemia in NIDDM patients, and, in *asymptomatic* obese NIDDM patients, they are not consistently effective either in decreasing the hyperglycemia or in maintaining the commonly recommended target levels of plasma glucose. Other authorities place a priority on avoiding

DIABETES MELLITUS (DM)

(See also DIABETES MELLITUS in Ch. 91)

DM is a genetically and clinically heterogeneous group of disorders that have carbohydrate intolerance in common. In pregnant women, the syndrome should be defined and classified as accurately as possible, because the complex metabolic alterations of normal gestation complicate diabetic control and may place the fetus in jeopardy. Thus, management of women with different types of DM should be individualized. In contemporary perinatal and neonatal centers, with preconception counseling and early prenatal care, the risks for diabetic mothers and their infants no longer exceed those for nondiabetic women. A successful diabetic pregnancy requires (1) preconception counseling and optimal diabetic control before, during, and after the pregnancy as well as meticulous management by a diabetes team or an obstetrician, internist, or family physician well versed in DM in pregnancy and by a pediatrician; (2) prompt diagnosis and treatment of both trivial and serious complications of pregnancy; (3) careful timing and appropriate mode of delivery; (4) attendance at delivery of a pediatrician knowledgeable in assessing and caring for infants of diabetic mothers; and (5) proximity of a neonatal intensive care nursery.

Classification

Nomenclature based on that adopted by the National Diabetes Data Group and WHO is presented in TABLE 181–1. The previous classification of DM in pregnancy was based on age at onset, duration, and complications of the disease. **Gestational diabetes (GDM)** is *carbohydrate intolerance of variable severity with onset or first recognition during the present pregnancy.* All pregnant women should be screened for GDM because unrecognized or untreated gestational carbohydrate intolerance is associated with increased fetal and neonatal loss and higher neonatal and maternal morbidity (see also PRENATAL CARE in Ch. 178). GDM occurs in 1 to 3% of all pregnancies, although the figure may be much higher in selected populations (eg, Mexican-Americans, American Indians, Orientals, Indians, Pacific Islanders). Pregnancy is a metabolic stress test for DM; women who fail the test and develop GDM may be obese, hyperinsulinemic, and insulin-resistant or thin and relatively insulin-deficient. Thus, GDM is also a heterogeneous syndrome.

Management of Diabetic Pregnancies

Good control of DM at conception and throughout gestation is important for an optimal maternal and infant outcome. Most diabetes centers use a team approach that combines the skills of physicians, nurses, nutritionists, and social workers. In addition, regional perinatal centers have experts in ophthalmology, renal disease, neurology, cardiology, anesthesiology, perinatology, and neonatology readily available.

Preconception counseling and diabetes control are important because congenital malformations in pregnancy complicated by DM may be linked to disturbances in maternal metabolism during the period of embryogenesis, and organogenesis is completed by the 6th or 7th wk of gestation.

TABLE 181–2 is a simple guide for managing pregnant women with type I (insulin-dependent diabetes mellitus [IDDM]), type II (non–insulin-dependent diabetes mellitus [NIDDM], but always **insulin-requiring** during gestation), and gestational carbohydrate intolerance (GCI) disorders. Details of treatment vary from one center to another, and patient care must be individualized.

In type I patients, **overinsulinization** is a risk of tight metabolic control regardless of the route of administration. In some type I patients, hypoglycemia does not trigger the normal release of counterregulatory hormones (catecholamines, glucagon, cortisol, and growth hormone). In these individuals, hypoglycemic coma may occur *with no premonitory symptoms.* All such patients should have glucagon kits and should be instructed (as should their families) in giving subcutaneous injection of glucagon for severe hypoglycemia (unconsciousness, confusion, or plasma glucose levels < 40 mg/dL). In pregnancy, good diabetic

TABLE 181–1. CLASSIFICATION OF GLUCOSE INTOLERANCE IN PREGNANT WOMEN

Nomenclature	*Former Names*	*Clinical Characteristics During Pregnancy*
Type I, insulin-dependent diabetes mellitus (IDDM)	Juvenile diabetes (JD) Juvenile-onset diabetes (JOD) Ketosis-prone diabetes Brittle diabetes	Ketosis-prone. Insulin-deficient because of islet cell loss. Often associated with specific HLA types with predisposition to viral insulitis or autoimmune (*islet cell antibody*) phenomena. Occurs at any age. Common in youth. These women are usually of normal weight but may be obese
Type II, non–insulin-dependent diabetes mellitus (NIDDM) Nonobese Obese Maturity-onset diabetes of youth (MODY)	Adult-onset diabetes (AOD) Maturity-onset diabetes (MOD) Ketosis-resistant diabetes Stable diabetes	Ketosis-resistant. More frequent in adults but occurs at any age. Majority are overweight. May be seen in family aggregates as an autosomal dominant genetic trait. *Always require insulin for hyperglycemia during pregnancy.* Previous history of "borderline diabetes," impaired glucose tolerance, or treatment with oral hypoglycemic agents. Hb A_{1c} elevated ≤ 20 wk gestation*
Type III, gestational carbohydrate intolerance (GCI)† Nonobese Obese	Gestational diabetes mellitus (GDM)	Screening tests: All pregnant women. 50-gm oral glucose load given randomly (need not be fasting) at 24–28 wk gestation. A plasma glucose value 1 h later ≥ 140 mg/dL (7.8 mmol/L) is an indication for a 3-h oral glucose tolerance test (OGTT) with 100 gm glucose
Type IV, secondary diabetes	Conditions and syndromes associated with impaired glucose tolerance	Cystic fibrosis; endocrine disorders—eg, acromegaly, hyperprolactinemia, Cushing's syndrome; drugs or chemical agents; renal dialysis; organ transplantations; certain genetic syndromes

* Laboratory methods and normal values vary. Women with gestational carbohydrate intolerance have normal Hb A_{1c} concentrations during the first half of pregnancy.

† All pregnant women at higher risk for gestational carbohydrate intolerance should be screened at the first prenatal visit. Risk factors are glycosuria, family history of diabetes in a first-degree relative, history of an unexplained fetal demise or stillbirth in a previous pregnancy, a previous heavy-for-date baby, obesity (body mass index [kg ÷ m^2] > 30), maternal age > 35 yr, or parity of 5 or more.

Diagnosis of GDM based on National Diabetes Data Group criteria (with a 100-gm glucose load) that 2 or more of the following plasma glucose values be met or exceeded: Fasting, 105 mg/dL (5.8 mmol/L); 1-h, 190 mg/dL (10.5 mmol/L); 2-h, 165 mg/dL (9.1 mmol/L); 3-h, 145 mg/dL (8.0 mmol/L).

Diagnosis of GDM based on 1985 WHO criteria (for pregnant and nonpregnant women) for impaired glucose tolerance following a 75-gm glucose challenge: Venous plasma glucose levels—fasting, < 140 mg/dL (7.8 mmol/L); 2-h, 140–200 mg/dL (7.8–11.1 mmol/L). For diabetes: venous plasma glucose levels—fasting, ≥ 140 mg/dL (7.8 mmol/L); 2-h, ≥ 200 mg/dL (11.1 mmol/L).

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TABLE 181–2. MANAGEMENT OF DIABETES MELLITUS IN PREGNANCY

Type	*Care Before Conception*	*Prenatal Care*	*Labor and Delivery*
I*	Regulate diabetes Hb A_{1c} concentration should be ≤ 8% at conception† Check for renal, retinal, and cardiac complications	Start care after missed period Recommend prenatal clinic visits each week Individualize diet following 1979 ADA guidelines and coordinate with insulin administration Recommend 3 meals and 3 snacks/day; emphasize consistent timing Individualize amount and type of insulin. In AM, 2/3 of total dosage (60% NPH, 40% regular); in PM, 1/3 (50% NPH, 50% regular)‡ Instruct in home blood-glucose monitoring Check Hb A_{1c} level every 4–6 wk Caution about dangers of hypoglycemia during exercise and at night Instruct patient and family in glucagon administration Perform fetal monitoring with nonstress tests, biophysical profiles, and kick counts from 35 wk to term (or earlier if indicated)	Deliver vaginally at term if patient has well-documented dating criteria and good diabetic control; amniocentesis may not be required. Deliver by cesarean section if perinatal complications are present, dating criteria are poor, prenatal care is inadequate, or diabetic control is poor; perform amniocentesis for mature lecithin/sphingomyelin ratio (≥ 2) and phosphatidylglycerol (≥ 3%) Deliver with constant low-dose insulin infusion, or alternatively, give usual PM NPH insulin dose and withhold insulin on AM of labor induction. Administer regular insulin s.c. as needed during labor and delivery Arrange for transitional and postpartum diabetes care
II*	Encourage weight loss if patient is obese (BMI > 27) Control hyperglycemia§ Hb A_{1c} concentration should be ≤ 8% at conception† Recommend diet low in fat, relatively high in complex carbohydrates, high in dietary fiber Encourage exercise	*Individualize* amount and type of insulin. For obese patients: Prescribe regular insulin before each meal. For normal-weight patients: In AM, 2/3 of total dosage (60% NPH, 40% regular); in PM, 1/3 (50% NPH, 50% regular). Use highly purified pork or human insulin *Individualize* daily caloric intake to avoid excessive weight gain (> 9 kg, or > 20 lb) in obese patients Discourage daytime snacks for obese patients Recommend moderate walking exercise after meals Instruct in home blood-glucose monitoring Monitor weekly at clinic visits: 2-h postbreakfast plasma glucose level Check Hb A_{1c} level every 4–6 wk	Same as for type I
Gestational	No special care unless patient has a history of GDM; then try to achieve normal weight, encourage modest exercise, check FBG and Hb A_{1c}	Modify diet: Eliminate concentrated sweets, monitor caloric intake to prevent excessive weight gain (> 9 kg, or > 20 lb) Discourage daytime snacks for obese patients Recommend moderate exercise after meals Prescribe small doses of purified pork or human short-acting insulin before meals if postprandial plasma glucose levels are > 120 mg/dL Monitor weekly at clinic visits: 2-h postbreakfast plasma glucose level	Deliver at term; avoid prolonged gestation (> 42 wk)

ADA = American Diabetes Association; NPH = neutral protamine Hagedorn; BMI = body mass index; GDM = gestational diabetes mellitus; FBG = fasting blood glucose.

* Suggested guidelines only; marked individual variations require appropriate adjustments.

† Normal values may differ, depending on laboratory methods used.

‡ Some hospital programs recommend up to 4 daily insulin injections. Continuous s.c. insulin infusion (CSII) given in medical research settings is a possible alternative. This is labor-intensive and should be used only in special circumstances and at a diabetes center.

§ Women taking oral hypoglycemics should discontinue them and control plasma glucose levels with insulin; possible adverse effects on fetal development due to oral agents cannot be excluded.

control consists of *absence* of wide glucose excursions with marked hyper- or hypoglycemia, Hb A_{1c} concentration of < 8%, and quantitative urinary glucose loss of < 1 gm/day. During pregnancy, normal fasting blood glucose levels are about 76 mg/dL (4.2 mmol/L), and 2-h postprandial values are ≤ 120 mg/dL (6.6 mmol/L). Purified pork and human insulin (as opposed to beef) are recommended during pregnancy to minimize antibody formation. Insulin antibodies cross the placenta, but their effect (if any) on the fetus is unknown.

Complications of Diabetic Pregnancies

Medical and obstetric complications such as infection, diabetic ketoacidosis, preterm labor, and pregnancy-induced hypertension are managed by current perinatal principles. No differences have been found in prevalence or severity of retinopathy, nephropathy, or neuropathy in diabetic women who have or have not experienced pregnancy. Diabetic retinopathy and nephropathy are not contraindications for conception or reasons for terminating pregnancy, but they require preconception counseling and close management before and during gestation. Initial and monthly ophthalmologic examinations are recommended. When proliferative retinopathy is noted at the first prenatal visit, the patient should receive photocoagulation treatment as soon as possible to prevent progressive deterioration. Women who have background retinopathy are followed expectantly.

No evidence indicates that diabetic renal disease worsens because of pregnancy, and renal complications during pregnancy are rare. Women with chronic renal failure who are undergoing hemodialysis rarely have a successful pregnancy, but surviving infants have been reported. One of 50 women who have functional renal transplants becomes pregnant. Pregnancy-induced hypertension occurs in 25% of such pregnancies, and other complications are common. The incidence of preterm births is related to maternal renal function and time interval from transplantation; the best prognosis for term deliveries of normal-birth-weight infants is ≥ 2 yr after transplantation.

In type I or II diabetic pregnancies, the major cause of neonatal mortality is congenital malformation incompatible with life. Therefore, a maternal serum α-fetoprotein determination is recommended at 16 to 18 wk gestation and a thorough ultrasound examination at 20 to 22 wk (with measurement of amniotic fluid α-fetoprotein level if the maternal serum value was abnormal). Abnormal maternal serum and amniotic fluid tests or an abnormal ultrasound examination suggests neural tube or other developmental defects. Fetal echocardiography should be performed if the Hb A_{1c} value was abnormally high in the first trimester or at the first prenatal visit. Congenital malformations of major organs have been positively correlated with elevated Hb A_{1c} concentrations at conception and during embryogenesis (the first 8 wk). In women with type II DM, use of oral hypoglycemic agents in the first trimester has been associated with cardiac defects, ear malformations, and the VATER anomaly.

Labor and Delivery

During the 3rd trimester, the 3 major aspects of care for diabetic women are control of maternal plasma glucose concentration, assessment of fetal well-being, and determination of fetal pulmonary maturation.

Most women with **GDM** have spontaneous onset of labor at term and are delivered vaginally. When induction of labor is necessary, it is initiated with IV oxytocin and amniotomy. If these pregnancies are permitted to go beyond term (> 42 wk), the fetus is at risk for death in utero. Even when maternal glucose levels in GDM have been normal or nearly so throughout pregnancy, infants are at risk for macrosomia. Thus, cesarean section may be necessary in case of dysfunctional labor or cephalopelvic disproportion or to avoid shoulder dystocia and injury to the infant and the birth canal.

In DM types I and II, the obstetrician should assess fetal well-being at 35 wk by external fetal heart rate monitoring (nonstress tests) and biophysical profiles. In addition, the patient should be instructed to count fetal movements for 30 min daily; a sudden decrease should be reported immediately to the obstetrician. Nonstress tests may begin earlier in women

TABLE 181–3. MANAGEMENT OF DIABETES DURING LABOR AND DELIVERY*

One day before induction of labor
Give usual insulin dose and diet to maintain euglycemia
Morning of induction†
Withhold insulin and breakfast
Measure baseline fasting blood glucose
Initiate labor and delivery flow sheet
Start IV infusion of 5% dextrose in 0.5% sodium chloride at 125 mL/h, using an infusion pump
During labor
Measure blood glucose hourly with meter at bedside‡
For glucose level > 110 mg/dL (6.1 mmol/L), add 10 U regular insulin to 1000 mL 5% dextrose in 0.5% sodium chloride and continue infusion rate of 125 mL/h (1.25 U insulin/h); *keep infusion rate constant*
Adjust insulin hourly, if necessary, by doubling or halving the insulin concentration to maintain blood glucose at 70–120 mg/dL (3.8–6.6 mmol/L)

* This protocol for women with insulin-dependent and non–insulin-dependent diabetes mellitus is adapted from Coustan (1988).

† For spontaneous labor, follow the same procedure. Insulin requirement will be less if the patient has taken intermediate-acting insulin in the previous 12 h. Patients with fever or infection will require higher doses (see TABLE 181–4).

‡ Obese patients with non–insulin-dependent diabetes mellitus who have required > 100 U of insulin/day prepartum, and patients with fever, infection, or other complications, will require higher insulin doses.

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with complications such as hypertension, hydramnios, premature rupture of membranes, intrauterine growth retardation, preterm labor, infection, or developmental defects.

Most diabetologists and perinatologists do not measure maternal serum or urinary estriol levels, since these expensive assays are not the most practical or useful tests for assessing fetal well-being.

Amniocentesis is not routinely performed to assess fetal lung maturity in women whose DM is well controlled and who have well-documented dating criteria. In these patients, spontaneous vaginal delivery at term is more common. Vaginal delivery is planned unless labor fails to progress, marked fetal macrosomia is present, or the patient has had a previous cesarean section and a trial labor is considered undesirable or unwanted by the patient. However, in women with obstetric complications, inadequate prenatal care, or poor diabetic control, amniocentesis is often necessary to assess fetal lung maturity. In these patients, the rate of cesarean sections is ≥ 50%.

Control of plasma glucose levels during labor and delivery is easier when insulin is administered as a continuous, low-dose infusion during the intrapartum period (see TABLES 181–3 and 181–4). The patient is hospitalized one day before delivery and given her usual diet and insulin dose. The following morning, breakfast and insulin are withheld and an IV infusion of 5% dextrose in 0.5% sodium chloride is started at 125 mL/h, using an infusion pump. Plasma glucose values are checked hourly, and the insulin dose is closely monitored to maintain normal glucose levels (70 to 120 mg/dL [3.8 to 6.6 mmol/L]). A pediatrician should attend the delivery to assess and care for the infant.

Postpartum Care

An immediate decrease in insulin requirement after delivery is related to the abrupt loss of the placenta, which has synthesized high levels of peptide and steroid hormones throughout pregnancy. In the immediate postpartum period, women with GDM and many of those with type II DM require no insulin. In type I patients, insulin requirements decline dramatically but gradually increase after about 72 h.